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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

28765 7590 12/07/2009

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EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
12/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13,15-31,37,40-47 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15-31,37,40-47 and 56-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-11, 13, 15-31, 37, 40-47 and 56-68 are pending and will presently be examined on the merits for patentability. No claim is allowed at this time.

Response to Arguments

Applicant's Remarks filed 31 August 2009 have been fully considered but they are not persuasive as discussed herein below.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 5-7, 11, 13, 26, 37, 40-42, 46, 47, 56-58, 60-63 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

gel formulations for the transdermal or transmucosal administration of an ***androgen, estrogen or progestin***, does not reasonably provide enablement for gel formulations for the transdermal or transmucosal administration of ***any active agent***. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention
2) the state of the prior art
3) the relative skill of those in the art
4) the predictability of the art
5) the breadth of the claims
6) the amount of direction or guidance provided
7) the presence or absence of working examples
8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The nature of the invention

The claimed invention relates to a gel formulation for the transdermal or transmucosal administration of an active agent comprising and active agent, a gelling agent, an alkanol, a polyalcohol, and a monoalkyl ether of diethylene glycol, wherein the

formulation is substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty esters.

The predictability of the art

WO 02/11768 A1, which has the common inventor Carrara, states:

> It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs. That is also concluded after careful analysis of the scientific literature relating to this specific topics, such as "Transdermal Therapeutic Systemic Medications, Marcel Dekker Inc., New York, 1989" (see table on page 3).
>
> Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work. (Page 2, lines 20-29)
>
> As it is well described in the literature of the art, there is not obviousness regarding the use of penetration enhancers to administer a drug(s) by transdermal route. As it is mentioned by W. R. Pfister in its chapter on "Transdermal and Dermal Therapeutic Systems: Current Status"in"Transdermal and Topical Drug Delivery Systems", Interpharm Press Inc., Buffalo Grove Illinois, 1997, pages 33-112, no general guidelines exist that will ensure success in selecting an appropriate enhancer for a specific drug to be delivered from a transdermal device (Hsieh 1994). The science of optimizing topical formulations is not predictive from one drug to another and permeation enhancers can produce a wide range of enhancement factors across drugs having different physicochemical properties. Rather, this is a process that requires extensive experimental work.
>
> It is also important to mention that transdermal permeability is mainly influenced by both physicochemical properties of the permeants and by the interaction of the permeants with the enhancers. Therefore a given enhancer could prove to be very adequate for a drug and simultaneously would not increase the permeability of the other compound. This is well illustrated by Chien, in its chapter on "Developmental Concepts and Practice in Transdermal Therapeutic Systems" in Transdermal Controlled Systemic Medications, Marcel Dekker Inc., New York, 1987, pages 25-81, who states that a penetration enhancer increases the permeation of different compound to different degree.
>
> There has not been known an enhancer or combination thereof which shows the transdermal penetration enhancement effect for any active agent or drug… (Page 4, lines 6-27)
>
> Additionally, another argument in favor of our position is sustained when the results reported by Chien are analyzed. He published the dependence of the enhancement factor for the skin permeation of progesterone on the alkyl chain length of saturated fatty acid in "Transdermal Controlled Systemic Medications". He found the major enhancement effect using caproic acid (C8), however the same author discloses in US patent 5,145,682 that the better enhancer for estradiol is decanoic acid (C10). These results lead us to attain the same conclusion of Chien in "Transdermal Controlled Systemic Medications", Marcel Dekker, New York 1987, pages 25-81, that concludes that the efficacy of skin penetration enhancer for a specific active agent, is function of the type, concentration and, how the penetration enhancer release from the devices.

> The prior art presented herein clearly prove that at least for some compounds, as shown in the present patent application, there is no such an universal penetration enhancer composition and the adequate permeation rate across the skin can be achieved only by testing different types of compounds at different concentrations. (Page 5, lines 4-20)

Therefore, Carrara clearly teaches that penetration enhancement is not predictive from one active agent to the next for a given penetration system.

Also, US 7,030,104 (Gray et al.) discloses:

> Trials of this invention attest that the concentration of each component and its interaction with the other components of a cutaneous gel formulation can, surprisingly, lead to a synergy or, on the contrary, to an inhibition of the quantity of active ingredients which pass through by the percutaneous route. Because of this, the preparations previously described for the percutaneous passage of a synthetic progestogen on its own, as described, are not directly applicable to an estrogen-progestogen combination as each combination of this type requires a specific galenic solution… (Column 19, lines 38-49)
>
> The nature of the absorption promoter ensuring adequate percutaneous passage for each active ingredient is not foreseeable… (Column 19, lines 56-58)
>
> The optimal ratio between the solvent and the passage promoter must be determined for each formulation… (Column 19, lines 63-64)

Therefore, Gray et al. clearly teach that each component of a cutaneous gel formulation affects the efficacy of percutaneous administration.

The breadth of the claims

The claims are broadly drawn to any active agent.

The amount of direction or guidance provided

The specification does not provide direction or guidance with respect to knowing whether the penetration enhancers will work for all active agents.

The presence or absence of working examples

The specification provides examples wherein estradiol, testosterone and estrone are combined with penetration enhancer according to the instant invention. However, the specification does not provide examples of other active agents.

The quantity of experimentation necessary

According to WO 02/11768, the usefulness of a particular compound(s) or mixtures thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work. Therefore, undue experimentation would be required to determine if the compositions according to the instant invention work for all active agents.

Therefore, for the aforementioned reasons, the Applicant is enabled for gel formulations for the transdermal or transmucosal administration of an ***androgen, estrogen or progestin***, but is not reasonably enabled for gel formulations for the transdermal or transmucosal administration of ***any active agent***.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1, 3-11, 13, 15-31, 37, 40-47 and 56-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite or depend from a claim that recites “between about” in references to concentration ranges, “from about”… “to about” in reference to effective dosage amounts, and “to about” in reference to serum levels. However, “between”, “from… to”, and “to…” implies a specific range with definite end values, whereas “about”

encompasses other values close to the end values. Therefore, the scopes of the ranges are not clearly defined.

2. Claims 7, 60, 66 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7 and 60 recite "monoalkyl ether of diethylene *ether*". However, this recitation is not consistent with "monoalkyl ether of diethylene *glycol*", which applicants recite throughout the specification and claims. It is not clear if applicants intended to recite "monoalkyl ether of diethylene glycol". For the purposes of search and examination, the instant claims are being construed as reciting "monoalkyl ether of diethylene glycol".

3. Claims 28 and 43-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 recites that the *active agent* includes estradiol in combination with a progestin. However, claim 1, which claim 28 is dependent from, states that when the active agent is estrogen, progestin is not present in the formulation in a therapeutically effective amount. Therefore, if the active agent is estrogen, progestin cannot be an active in the formulation. However, claim 28 recites that estradiol (an estrogen) and progestin are both actives present in combination. Claims 43-45 are similar to claim 28 in that they claim a combination of estrogen and progestin as *active agents*, whereas claim 37 states that estrogen and progestin cannot

both be active agents in the same formulation (one present as active whereas the other is present in an amount that is not therapeutically effective, i.e. not active).

4. Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 59 recites the limitation "The gel formulation of claim 37" in the 1st line. However, claim 37 does not recite that the formulation is in the form of a gel. In fact, claim 47 recites that the formulation of claim 37 can be in the form of a gel, lotion, cream, spray, aerosol, ointment, emulsion, suspension, liposomal system, lacquer, patch, bandage, or occlusive dressing. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1, 5-7, 11, 37, 40-42, 46, 47, 60 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768 A1).

Carrara et al. disclose a composition comprising 1.25 wt.% testosterone, 5.00 wt.% diethylene glycol monoethyl ether (Transcutol P), 5.95 wt.% propylene glycol, 43.09 wt.% ethyl alcohol, 43.07 wt.% water, 1.20 wt.% carbomer (Carbopol 980 NF, a gelling agent), 0.38 wt.% triethanolamine (a neutralizing agent), and 0.059 wt.% disodium EDTA (a sequestering agent) (Example 2).

As noted by Applicants on page 11 of their response filed 10 November 2008, Example 2 of Carrara et al. does not contain a long chain fatty alcohol or long chain fatty acid.

Response to Arguments

Applicants argue on page 12 that claim 1 as amended now recites that when the formulation comprises testosterone, it is not used as the sole active agent or if it is the sole agent it is present in an amount of 1 wt% or less, and there is no teaching or suggestion in Carrara to modify the comparative formulations. Thus, Carrara does not teach or suggest the presently claimed invention. However, the examiner respectfully argues that the specification and the instant claims do not define “active ingredient”. Carrara et al. disclose the composition comprising 1.25 wt.% testosterone, 43.09 wt.% ethyl alcohol, and 0.059 wt.% disodium EDTA. It is well-known in the art that ethyl alcohol and disodium EDTA are antimicrobial agents. Therefore, Carrara et al. clearly disclose a composition wherein testosterone is not the only active ingredient.

2. Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 26, 28, 37, 40-43, 45-47, 56, 57, 60-62 and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Gray et al. (WO 02/22132; US 7,030,104 is the English-language equivalent and is relied upon herein).

Gray et al. disclose gel formulations (Table 1) for percutaneous administration wherein the gels comprise:

NAc (nomegestrol acetate)	0.4	0.4	—
Estradiol	—	0.1	0.1
Carbopol 1342 or 1382	0.5	0.5	0.5
Propyleneglycol	6	6	6
Transcutol	5	5	5
Soiketal			
EDTA	0.05	0.05	0.05
Triethanolamine	0.3	0.3	0.3
Demineralized water	42.75	42.65	43.05
95° Ethanol	45	45	45

Therefore, Gray et al. disclose a gel comprising a progestin (nomegestrol acetate), estrogen (estradiol) or a combination thereof at 0.1 to 0.5 wt.%, a gelling agent (Carbopol 1342 or 1382) at 0.5 wt.%, an alkanol (95° ethanol) at 45 wt.%, a polyalcohol (propylene glycol) at 6 wt.%, a permeation enhancer (Transcutol®: diethylene glycol monoethyl ether) at 5 wt.%, a neutralizing agent (triethanolamine) at 0.3 wt.%; a sequestering agent (EDTA) at 0.05 wt.%, and water at 42.65-43.05 wt.%.

Gray et al. disclose administering the gels to women to determine the pharmacokinetic behavior or percutaneous administration (col. 14, ln. 1-15).

3. Claims 1, 3-8, 10, 11, 13, 15, 20, 22, 26, 28, 37, 40-43, 45-47, 56, 57, 60-62 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Gray et al. (US 7,030,104) for the same reasons as above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1, 3-11, 13, 15-20, 22, 26, 28, 29, 31, 37, 40-47, 56-63 and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 02/22132; US 7,030,104 is the English-language equivalent and is relied upon herein), in view of Dudley et al. (US 6,503,894), Labrie (US 5,955,455) and Bechgaard et al. (US 5,397,771).

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Gray et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Gray et al. do not teach treating hypogonadism, or the administration of methyltestosterone with methandrostenolone. However, Dudley et al. teach a gel formulation for the treatment of hypogonadism comprising an androgen, alcohol, and penetration enhancer (Abstract), wherein the androgens include testosterone, methyltestosterone, and methandrostenolone (col. 11, ln. 65-66; col. 12, ln. 1 and 17-22; and Table 5). Dudley et al. further teach that suitable penetration enhancers include diethylene glycol monoethyl ether (col. 12, ln. 54-55).

Also, Labrie teaches that dehydroepiandrosterone (DHEA) is useful for the treatment of hypogonadism and conditions related to decreased secretion of sex steroid precursors by the adrenals (Abstract).

Gray et al. also do not teach a kit comprising a container that retains their compositions and includes a pump, as instantly claimed. However, it would have been well within the purview of one of ordinary skill in the art to determine an appropriate dispensing device, such as a Pfeiffer pump unit delivering 50 when activated, as reasonably taught by Bechgaard et al. (col. 14, ln. 30-32).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Gray et al., using as the androgen testosterone, methyltestosterone, methandrostenolone, DHEA or combinations thereof, and as the penetration enhancer diethylene glycol monoethyl ether, as reasonably taught by Dudley et al.

With regard to the combination of methyltestosterone and methandrostenolone, such would have been obvious in the absence of evidence to the contrary because it is generally prima facie obvious to use in combination two or more ingredients that have previously been used separately for the same purpose to form a third composition useful for that same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to the dosage amount and serum levels of hormone, the amounts of hormone in the system that are effective to treat various conditions is well-known to one of ordinary skill in the art. Therefore, it would be within the level of ordinary skill to determine the amount of hormone necessary to achieve therapeutic serum levels. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of

percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 1, 3-8, 10, 11, 13, 15, 20-28, 37, 40-43, 45-47, 56, 57, 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 02/22132; US 7,030,104 is the English-language equivalent and is relied upon herein). in view of Catherino et al. (J. Steroid Biochem. Molec. Biol., 1995) and Carrara et al. (WO 02/11768).

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Gray et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Gray et al. do not teach the formulations comprising a progestin as listed in instant claim 21. However, Gray et al. teach formulations comprising nomegestrol acetate, which is a clinically useful 19-norprogesterone derivative according to Catherino et al. Catherino et al. teach that megestrol acetate and nomegestrol acetate differ only at the 19 position, and that nomegestrol is a clinically useful progestin and an effective contraceptive agent when used as an implant (pg. 239, right column, ln. 3-7; and pg. 243, left column, last line to right column, ln. 7). Thus, it would have been obvious for one of ordinary skill to substitute megestrol acetate in the place of nomegestrol acetate, as they differ only in the absence of a methyl at the 19 position and are both useful progestins.

Gray et al. also do not teach their formulations comprising testosterone in combination with estrone, estradiol, 17β-estradiol, ethynil estradiol, estriol succinate, estriol dihexanate or estriol sulfamate, as instantly claimed. However, Carrara et al. teach compositions comprising testosterone and 17β-estradiol, a penetration enhancer, an alkanol, a polyalcohol, a gelling agent and water (Examples 16-20). Therefore, it would have been prima facie obvious for one of ordinary skill in the art to formulate the compositions according to Gray et al. comprising testosterone and 17β-estradiol.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to formulate the compositions of Gray et al. comprising a

progestin according to claim 21, or a combination of testosterone and estrone, estradiol, 17β-estradiol, ethynil estradiol, estriol succinate, estriol dihexanate or estriol sulfamate.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616